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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/390,634	09/07/1999	PAUL J. PRICE	IVGN 166.1 DIV	7270

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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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02/07/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/390,634

Applicant(s)

PRICE ET AL.

Examiner

Anoop Singh

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 November 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 176,177,180,183-189,192,195-201,204-211,214,217-223,226-240,243-249,251-253,255-265,268-274,278 and 280-282.

Continuation of Disposition of Claims: Claims rejected are 176,177,180,183-189,192,195-201,204-211,214,217-223,226-240,243-249,251-253,255-265,268-274,278 and 280-282.

DETAILED ACTION

Applicant's amendment to the claims filed on November 19, 2007 has been received and entered. Claims 176, 210, 232, 249, 251, 253, 255, 263, 274, 276, 278 and 280 have been amended, while claims 1-175, 178-179, 181-182, 190-191, 193-194, 202-203, 212-213, 215-216, 224-225, 241-242, 250, 254, 266-267, 275-277 and 279 have been canceled.

Claims 176-177, 180, 183-189, 192, 195-201, 204-211, 214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 278, 280-281 and 282 are under consideration.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ponting (US Patent 5,405,772, IDS), Gibco BRL Products and Reference Guide ((1997) Chapters 5 and 8, art of record) and Atsumi et al. (Develop. Growth & Differ. 35(1):81-87, 1993, art of record) for the reasons of record.

Claims 176-177, 180, 183-189, 192, 195-201, 204-211, 214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 278, 280-281 and 282 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ponting (US Patent 5,405,772, art of record), Gibco BRL Products and Reference Guide ((1997), art of record), Atsumi et al. (Develop. Growth & Differ. 35(1): 81-87, 1993, art of record) and Nichols et al (Exp Cell Res. 1994; 215(1):237-9, IDS) for the reasons of record.

Applicants argue that cited references: (i) fail to provide all elements of the claims; 2) fails to provide any motivation or suggestion to combine the elements of the present claims in the manner claimed. Applicants assert that Ponting et al do not teach medium capable of preventing differentiation of mouse ES cell during expansion (see page 18 of the argument). Applicants also argue the combination of claimed elements by citing *KSR Int 'I v. Teleflex Inc.*, 550 U.S. at, Slip Op. at 1-24 (Apr. 30, 2007) (No. 04-1350) that has provided guidance for assessing whether an invention is obvious and has indicated that merely collecting "building blocks" does not provide a reason that would prompt one of skill in the art to arrive at the claimed invention.

Applicant's arguments have been fully considered, but found not persuasive.

With respect to applicants argument that none of the reference teaches serum free cell culture medium prevents differentiation, it is noted that contrary to applicants assertion preventing differentiation of ES cells is not obtained by synthetic serum disclosed by Ponting, rather it is obtained by providing LIF to the culture which is clearly known in the prior art as evidenced by Atsumi. In response to applicant's arguments against the references individually that neither Ponting teaches nor suggest cell culture medium that prevents differentiation of mouse ES cell during expansion (see page 18), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). To the contrary, each reference provides conditions to maintain ES cells in an undifferentiated state. As stated in previous office actions serum causes differentiation and not the basal media. Ponting provided a synthetic media and guidance to obtain a media that would expand mammalian cells undifferentiated ES cells. Moreover, it is noted that other factors besides the generality of the media, such as the presence of LIF for mouse ES cells in feeder free conditions, that provides the condition wherein ES cells do not differentiate. The combination of cited references provides the necessary guidance and details for providing a synthetic serum supplement. GIBCO reference provided specific compounds to be added to the media such as LIF, SF, lipid-rich/poor albumin, iron-saturated transferrin, it is noted that these elements were commercially available at the time of filing (for example page 15 of the instant specification) and also evidenced by Gibco BRL Products and Reference Guide. It is noted that Ponting teaches that the media should be as defined as possible and optimized for a given cell type, therefore one of ordinary skill in the art would be motivated to use and test the various forms of these components for their specific affects on the cells in culture. For example, lipid-rich/poor albumin provides a more defined source of albumin, lacking lipids that could affect the cells. Moreover,

Ponting teaches that the components can be natural or synthetic (column 11, lines 65-68), wherein a synthetic component would represent a more defined molecule free from potential contaminants that may be present in naturally isolated sources. It is notable although the media disclosed by Ponting generally embraces serum-free medium but Ponting indicated that certain well defined and highly purified component may be included. One of ordinary skill in the art would easily optimize to lipid-rich fraction of serum albumin by chromatographically purifying with a specific IgG content. Applicants further argue that Atsumi et al do not cure the deficiency of Ponting. As noted before, the art provides evidence that at the time of filing and issuance of Ponting serum-free conditions for culturing embryonic stem cells were known and used (see also Atsumi et al). Atsumi et al teach to use of a serum supplement serum-free media that are obtained as a conditioned media. Using such media, Atsumi et al. were able to define specific factors supplied by the feeder cells in order to make a complete serum-free media. Ponting clearly provides motivation of the specific embodiments required to make a synthetic serum supplement. Additionally, the reference of Nichols is included to demonstrate that functional equivalent of LIF such as oncostatin N, CNTF that prevents differentiation of ES cells even in presence of serum. While Ponting does not specifically disclose all the specific components listed in the claims, the use of these components would be prima facie obvious because they are factors commonly used in cell culture. Importantly, upon review of the present specification, there is no specific teaching that any one of the components recited or encompassed by the instant claims provides any unexpected affect on the cultured cells that would not have been readily known in the art, such as the use of LIF, oncostatin N, CNTF to prevent differentiation of embryonic stem cells in culture. The level of knowledge and skill in the art for culturing cells is high, and there would be a reasonable motivation and expectation of success to use specific components from various

sources as provided by Ponting, Atsumi, Nichols and GIBCO catalogue to provide for a more defined and optimized media.

Applicants also argue and cite Supreme Court case to suggest that cited references do not teach or suggest methods for preventing differentiation of embryonic stem cells and , there is no suggestion or motivation to combine elements to arrive at, *inter alia*, a serum-free cell culture medium which prevents differentiation of mouse embryonic stem cells during expansion.

In response, it is noted that examiner has previously described why one of ordinary skill in the art would be motivated to use a serum supplement serum-free media that are obtained as a conditioned media to define specific factors supplied by the feeder cells in order to make a complete serum-free media as exemplified by Atsumi et al. Ponting clearly provides motivation of the specific embodiments required to make a synthetic serum supplement particularly since there is no specific teaching that any one of the components recited or encompassed by the instant claims provides any unexpected affect on the cultured cells that would not have been readily known in the art. The method for preventing differentiation only require contacting and expanding of ES cells in serum free medium. As stated before, Examiner has also provided evidence to show that culturing ES cells in presence of the use of specific elements such as LIF, CNF or oncostatin M would prevent differentiation of embryonic stem cells in culture (see Atsumi and Nichols). Thus, contrary to applicant's argument several elements cited in the rejection were not merely known for some reasons rather they were known for specific use in either expansion or prevention of differentiation of ES cells. Moreover, with respect to applicants' argument of KSR, It is noted that a recent *KSR* forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). In the instant case, each of the claimed element is found within the scope and

content of prior art and one of ordinary skill in the art could have combined different elements in the medium disclosed by the Ponting, GIBCO, Atsumi and Nichols particularly since one of ordinary skill in the art would have recognized the resulting medium of the combination to be predictable in the preventing differentiation of mouse ES cell cultured in serum free medium when used in combination with LIF, oncostatin M, CNF or combination thereof. Specifically, Ponting teaches a medium for long-term proliferation and development of cells. Beyond basal media commercially available, Ponting provides guidance for obtaining serum free media (starting at column 14, line 57). Ponting teach specific components and preferred ranges thereof to include in the media (see for example Table in columns 12 and 13). Ponting teaches that the media can contain albumin (e.g. human or bovine), transferrin (e.g. human or bovine), growth factors, vitamins, antioxidants, insulin and various trace elements (see columns 9-10, tables and reduction to practice in working examples). Ponting teaches that the media disclosed can be used to culture a variety of cell types including embryonic stem cells (column 8, lines 13-15) including specific reference to known mouse embryonic stem cell lines. Further, Ponting teaches that general culturing methods known in the art can be used to culture a particular cell type, such as providing a feeder cell layer (column 8, lines 30-37). Finally, Ponting teaches that the cells can be used in a variety of methods including in the production of proteins in culture (column 16, lines 21-31 and 45-64) and methods of differentiation (see column 8, lines 32-42, lines 61-69 and working examples). Additionally, it is noted that media composition can be in a frozen state preparations. The invention disclosed by Ponting is to provide a completely defined media (column 1). Ponting teaches that the disclosed media can be used for variety of cell types and that the defined media 'makes possible the precise determination of the effect of a known molecule' (column 7, lines 44-50). Further, Ponting teaches that in determining the effective amount of any of the constituent components experimentation by methods known to a cell

culturist would have to be done (bridging columns 8-9 and generally supported by the working examples). Finally, Ponting teaches that specific conditions for culturing a particular cell type would have to be adapted by substituting the serum supplement to the methods and materials known in the art that would have been used for any particular cell type (starting in column 15, section E). Though Ponting does not specifically teach to use factors such as LIF, iron-saturated transferrin or lipid poor and recombinant albumin, these factors were readily available at the time of filing and used in cell culturing. The reference of Atsumi, GIBCO catalogue and Nichols teaches mouse embryonic stem cells required LIF and other functionally equivalent factors in the culture media to efficiently maintain their undifferentiated state during culturing. Therefore, given that serum free medium comprising lipid rich serum albumin and other differentiation inhibiting agent such as LIF, oncostatin M and CNTF were available for use to culture ES cells as per the teachings of Ponting, Atsumi, GIBCO and Nichols it would have obvious for to one of ordinary skill in the art to optimize the known elements in serum free culture medium with reasonable expectation of achieving predictable result in the preventing differentiation of mouse ES cell cultured in serum free medium.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Maurer ("Animal Cell Culture, A Practical Approach", pages 13-31, 1986, IDS) Maurer teaches commercially available serum-free media and supplements which are available for optimizing mammalian cell cultures (see page 28-29, and Table 3) including the use of serum-substitutes, such as insulin, transferrin, growth

factors, and hormones, for replacing the serum, as well as other supplements such as trace elements (see, page 25).

Rose et al (Cytokine, 1994, 48-54) teaches oncostatin M inhibits the differentiation of pluripotent stem cells under in vitro condition and extent of inhibition was comparable to effect seen with LIF.

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Primary Examiner
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